8e

Contains No CBI

INTERNATIONAL
INSTITUTE OF
SYNTHETIC RUBBER
PRODUCERS, INC.

93 SEP 14 PM 2:15

8EHQ-0993-12435

13 September 1993

Document Processing Center
Attn: TSCA 8 (e) Coordinator
Chemical Information Division
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M. Street, S.W.
Washington, D.C. 20460

Re: TSCA 8(e) Submittal

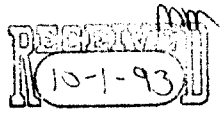
Dear Sir:

The International Institute of Synthetic Rubber Producers, Inc. (hereinafter, "IISRP") is submitting this notice pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA). This information is not confidential.

This TSCA 8(e) submission is made on behalf of the companies who are parties to the isoprene research being carried out at Battelle laboratories under sponsorship of the IISRP. These companies are: Chevron Chemical Company, Dow Chemical USA, EniChem Elastomeri SrL, Exxon Chemical Company, Goodyear Tire & Rubber Company, Polysar Rubber Corporation, Shell Chemical Company, and Shell International Chemical Co. Ltd.

This submittal relates to isoprene (CAS #78-79-5). A chronic inhalation oncogenicity study in B6C3F1 mice with isoprene is ongoing at Battelle laboratories in Columbus, Ohio. This study is sponsored by the IISRP. Prior related reports have been submitted to EPA under Section 8(e) by Chevron Chemical Company (see letter from John C. Litterio, February 3, 1993) and Shell Oil Company, (see letter from Roy D. Gerard, June 10, 1992).

The exposure and experimental design, which is summarized below, were intended to assess the effects of concentration, length of daily exposure, and duration of total exposure over the lifespan of the animals, as independent variables of the survival and ultimate oncogenicity of the test article.



2077 SOUTH GESSNER ROAD / SUITE 133 / HOUSTON, TEXAS 77063 / (713)-783-7511 / FAX (713) 783-7253

3 pgs.

CHRONIC INHALATION STUDY OF ISOPRENE IN MICE
Experimental Design

Test Article Concentration, ppm	Daily Exposure Hours	Numbers of Weeks Exposed	Number of Mice $B6C3F_1$
0	8	80	50M, 50F
10	8	80	50M, 50F
70	8	40	50M
70	8	80	50M, 50F
140	8	40	50M
280	8	20	50M
280	8	80	50M
700	8	80	50M
2200	4	20	50M
2200	4	80	50M
2200	8	40	50M
2200	8	80	50M

The in-life phase of this study ended in April of 1993. The total set of tissues from this study have not been fully evaluated or peer-reviewed, nor have final biostatistics been completed. Nonetheless, in a preliminary assessment of the histopathology and other post mortem data there appears to be an increased incidence of hemangiosarcomas and histiocytic sarcomas, and possibly lymphomas, tumor types not reported in the NTP inhalation study of isoprene in mice. In addition, the results of this study appear to confirm the exposure-related incidence of liver, lung, Harderian gland and forestomach tumors reported in the NTP study.

In addition to the above observations, cytogenetic experiments included as part of this study indicated a concentration-dependent increase in the incidence of micronuclei in exposed mice. When compared to controls and to those animals exposed to lower concentrations of isoprene, the percent increase in micronuclei persent in peripheral blood appeared to increase in animals exposed to concentrations of 280 ppm or greater for 80 weeks. Further, there appeared to be an exposure-related decrease in ovarian weights of female mice exposed to concentrations of 70 ppm of isoprene for 80 weeks compared to control mice. There may be an exposure related decrease in testicular weights at $\geq$700 ppm. Lastly, to confirm data previously reported to the Agency, the survival rates were lower in mice exposed to isoprene concentrations of 280 ppm and above for periods of 80 weeks. There were no apparent exposure-related effects on growth rate or the clinical condition of the animals.

We stress that these conclusions are preliminary and that statistical analyses are ongoing. The final report for the IISRP-sponsored isoprene study will be submitted when available. If you have any questions, please contact Michael G. Bird, Ph.D., Exxon Biomedical Sciences, Inc., Mettlers Road, CN 2350, East Millstone, New Jersey 08875-2350 (telephone 908/873 6067).

Sincerely,

William E. Tessmer
Managing Director

File ISO(E).VAR

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

JAN 25 199

William E. Tessner
Managing Director
International Institute of Synthetic Rubber Producers, Inc.
2077 South Gessner Road, Suite 133
Houston, Texas 77063

This letter formally acknowledges EPA's receipt of information submitted by your organization under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA Section 8(e) Document Control Number (i.e., 8EHQ-0000-0000 Init.) assigned by EPA to your submission(s). Please refer to this cited number when submitting follow-up or supplemental information.

Please note that all submitted correspondence will be placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA Section 8(e) policy statement (43 FR 11110, March 16, 1978).

Confidential submissions submitted pursuant to the TSCA Section 8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims, because substantiation of CBI claims is required at the same time the 8(e) CAP is submitted to EPA. (If not done so already, please ensure that this information is provided to the Agency). When substantiating any/all claims, answer the questions detailed in the following attachment.

For NON-CAP submissions, any confidentiality claims should be supported by submission of information as described in the attachment(s).

12435 A

Triage of 8(e) Submissions

Date sent to triage: JAN 28 1994

NON-CAP CAP

Submission number: 12435 A

TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Erne Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX (CTOX/ONCO) CTOX RTOX ~~GTOX~~

NEUR EPI IMMUNO (CYTO)

Other (FATE, EXPO, MET, etc.): _____

Notes:

For Contractor Use Only

entire document: 1 (2) 3 **pages** 1-3 **pages** 1-3

Notes:

Contractor reviewer : DMC **Date:** 1/12/94

TSCATS DATA:
submission # 88110 0993-12435 SEQ A

TYPE (INT) SUPP FLWP

SUBMITTER NAME: International Inst. of Synth. Rubber Producers, Inc.

INFORMATION REQUESTED: FLWP DATE
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)
DISPOSITION:
0 3 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 09/13/93 OTS DATE: 09/14/93 CSRAD DATE: 10/01/93

CHEMICAL NAME: | **CAS#**
78-79-5

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
(202)	ONCO (ANIMAL)	(01) 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243	CHEM/PHYS PROP	01 02 04
204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	(0245)	CLASTO (ANIMAL)	(01) 02 04
206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
(207)	REPRO/TERATO (ANIMAL)	(01) 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQUST DELAY	01 02 04	0248	PROD/USE/PROC	01 02 04
209	NEURO (ANIMAL)	01 02 04	0224	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0299	OTHER	01 02 04
211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
(215)	CHRONIC TOX (ANIMAL)	(01) 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

Ctox / Onco

TRIAGE DATA:

NON-CBI INVENTORY
(YES (CONTINUE))
NO (DROP)
DETERMINE

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER:

SPECIES
mus

TOXICOLOGICAL CONCERN:
LOW
MED
(HIGH)

USE:

PRODUCTION:

COMMENTS: Non-Cap

12435 Isoprene

CONCERN: HIGH

A chronic inhalation study of isoprene was conducted in B6C3F1 mice at levels of 10, 70, 140, 280, 700, or 2200 ppm. Exposure was 8 hours a day for all groups except the highest which was also tested at 4 hours/day. Duration of exposure was 80 weeks at each exposure level. In addition, at 70 and 140 ppm a 40-week exposure duration and at 280 and 2200 ppm 20-week exposure durations were also tested.

Preliminary assessment of histopathology, indicated an apparent increase in hemangiosarcomas and histiocytic sarcomas as well as an increase in lung, liver, Harderian gland and forestomach tumors.

5) 8EHQ-0993-612435 Init: Rank - medium.

Chemical: isoprene (CAS# 78-79-5).

Title of study, laboratory and date not given: Positive for chromosome mutations (micronuclei) in peripheral blood of mice exposed in vivo.